UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

COMPUTATIONAL TOXICOLOGY

Why Does the Environmental Protection Agency Study Toxicology?

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The Fundamental Idea of Toxicology

"All things are poison and nothing is without poison, only the dose permits something not to be poisonous."

Paracelsus
1493 - 1541

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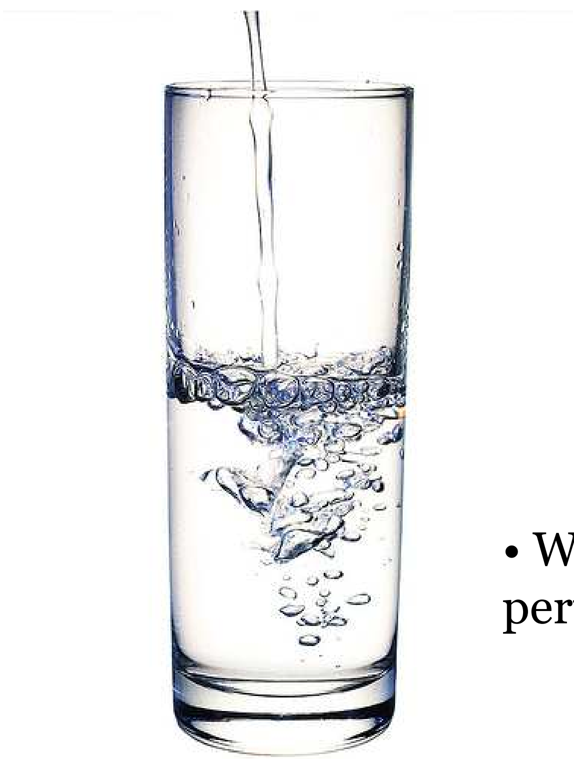
Dose makes the poison

- On January 12, 2007 a woman died of water intoxication after trying to win a Wii by drinking the most water



- We know that drinking normal amounts of water is perfectly safe:

Dose makes the poison

What is Toxicology?

• Toxicology tries to determine, for a given chemical, what amount of exposure to that chemical will cause a negative effect

• There can be many different exposures, including:

  - Food
  - Breathing
  - Bathing

• There can be many different effects, including:

  - Different types of cancers
  - Slowed development
  - Immediate sickness

Environmental Chemicals

- Toxicologists at the EPA investigates chemicals found in the environment

- We try to determine how much of a chemical is associated with negative effects

- Risk assessors then determine the allowable environmental concentrations

- In October 2006, National Geographic ran a story “The Chemicals Within Us” investigating the variety of chemicals found within one reporter’s blood

- According to the article, in the U.S. we make use of 82,000 different chemicals

- Some of these chemicals end up in the environment, and small amounts of many of these chemicals can end up inside us

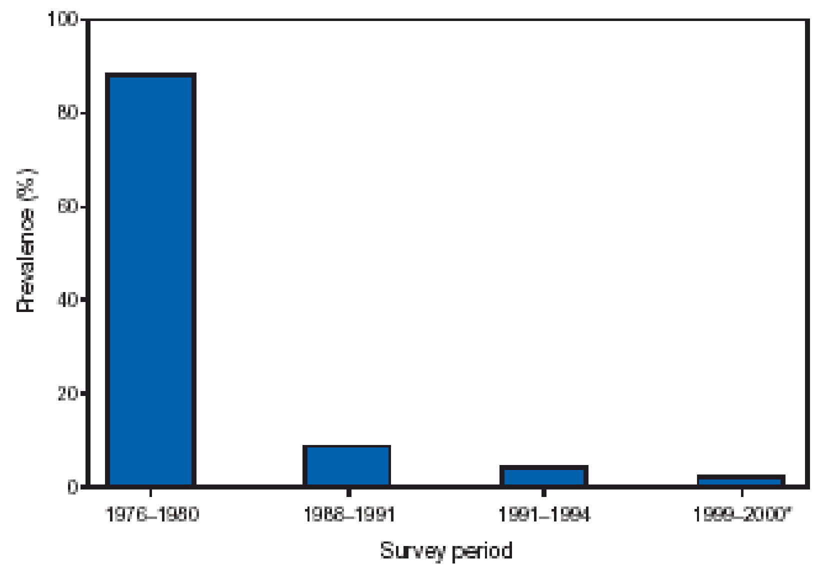
NHANES

• The Centers for Disease Control and Prevention (CDC) conducts the National Health and Nutrition Examination Survey (NHANES)

• Examines a wide range of aspects of Americans (like weight and nutrition), including blood levels of environmental chemicals

• For instance, blood levels of lead, which used to be added to gasoline, has sharply dropped since the U.S. started switching to unleaded gasoline in the 1970's

FIGURE 1. Blood lead levels ≥10 µg/dL among children aged 1–5 years — United States, 1976–1980, 1988–1991, 1991–1994, and 1999–2000*



Source: National Health and Nutrition Examination Surveys (NHANES).
Note: In 1991, NHANES III Phase 1 was completed and Phase 2 was begun.
* Data for 1999–2000 are highly variable (relative standard error >30%).

Meyer, et al., MMWR Surveillance Summaries (2003)

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How do you get exposed?

Images from National Geographic "The Chemicals Within Us"

- We get exposed to some chemicals just by breathing
- Some crops are sprayed with pesticides that can linger on the food if not washed
- In the United States, regulations control how much of a chemical is allowed

- There can be as many as 1700 new chemicals a year, and new uses for old chemicals as well
- The EPA investigates the impact of these chemicals on our health

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Google "The Chemicals Within Us" for more information

How Long do the Chemicals Stay in You?

• The National Geographic reporter's blood contained traces of several chemicals now banned or restricted that he may have been exposed to as a child, including DDT

• DDT was banned in the U.S. in 1972

• Part of toxicology is determining how long a chemical will stay within you

• Depending on the chemical, it may be excreted rapidly, or stored in different tissues

• The determination of the distribution and excretion of chemicals is called *toxicokinetics*

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What are Biological Models?

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This presentation was reviewed by EPA but does not necessarily reflect official Agency policy.

Models

• In science, a model is a simplification of reality that allows you to investigate how you think reality works

• By only including the parts that you think are important, you see if you can explain observations

• If you can't, you may have to add more parts to your model

•"All models are wrong and some are useful" – George Box, Professor of Statistics

Population Cycles

• Biological models can be used to understand complex interactions

• For instance, in the 1860's and 1870's trappers noticed that the Canadian snowshoe hair population was cycling

Schnell, et al., American Scientist (2007)

Ed Cesar/Photo Researchers, Inc.

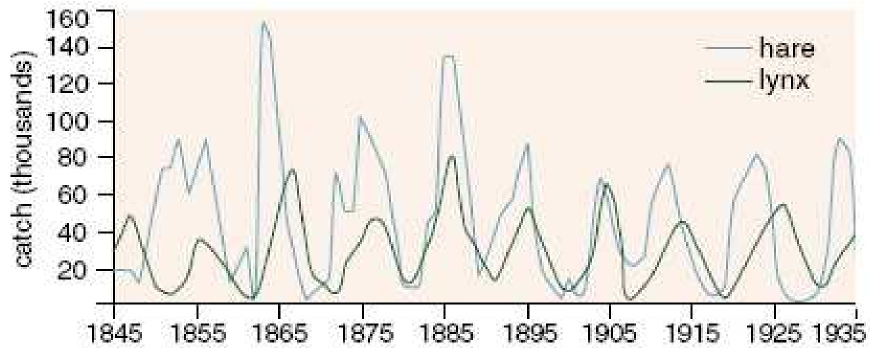

Figure 2. Early in the 20th century, Alfred Lotka and Vito Volterra developed equations now used by ecologists to understand predator-prey interactions. An example of predator-prey population dynamics is the record of annual Hudson Bay Company catches of Canadian lynx and snowshoe hares, which appears to show fluctuations on 9- to 11-year cycles. Through a combination of modeling and experiment, ecologists have found that these cycles can be predicted by a model including both predation *(left)* and changes in the hares' food supply. (Graph adapted from Eugene Odum's *Fundamentals of Ecology*, 1953.)

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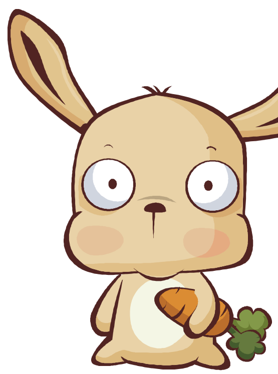
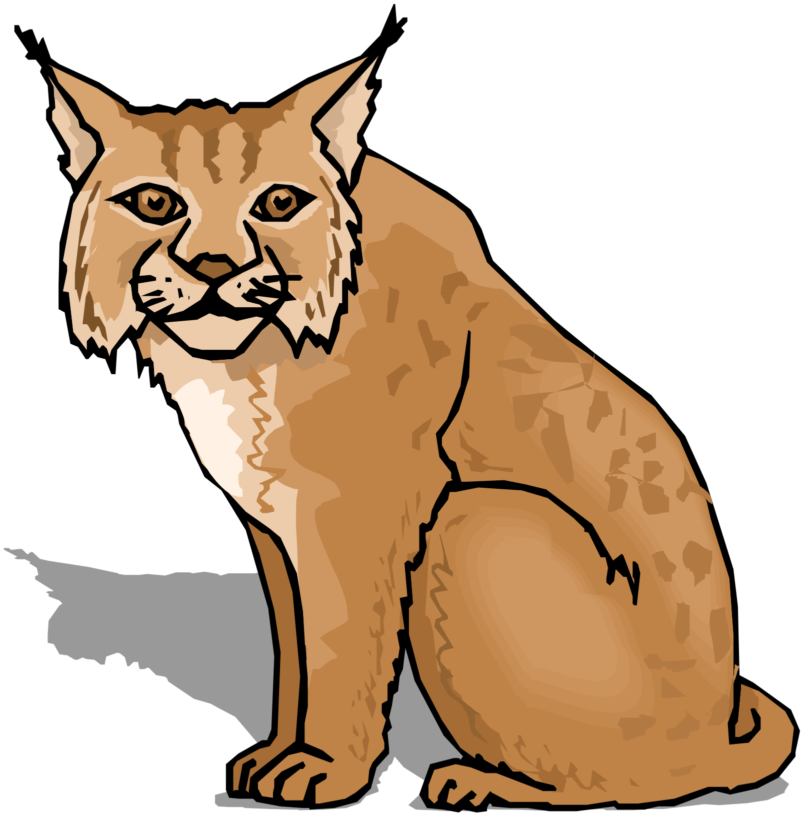
Rabbits and Lynx

- We can model this by including very few effects:
- First, rabbits make more rabbits…





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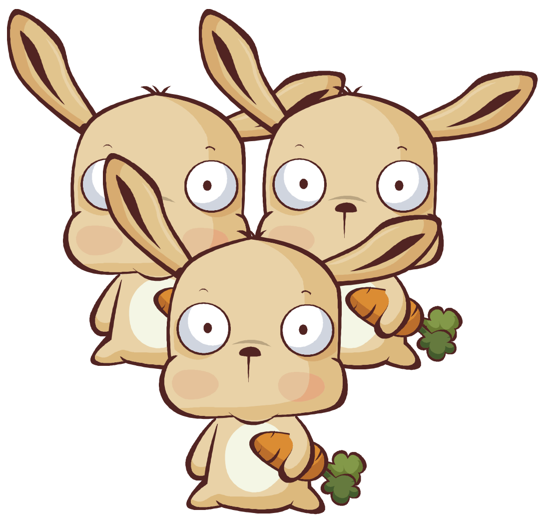
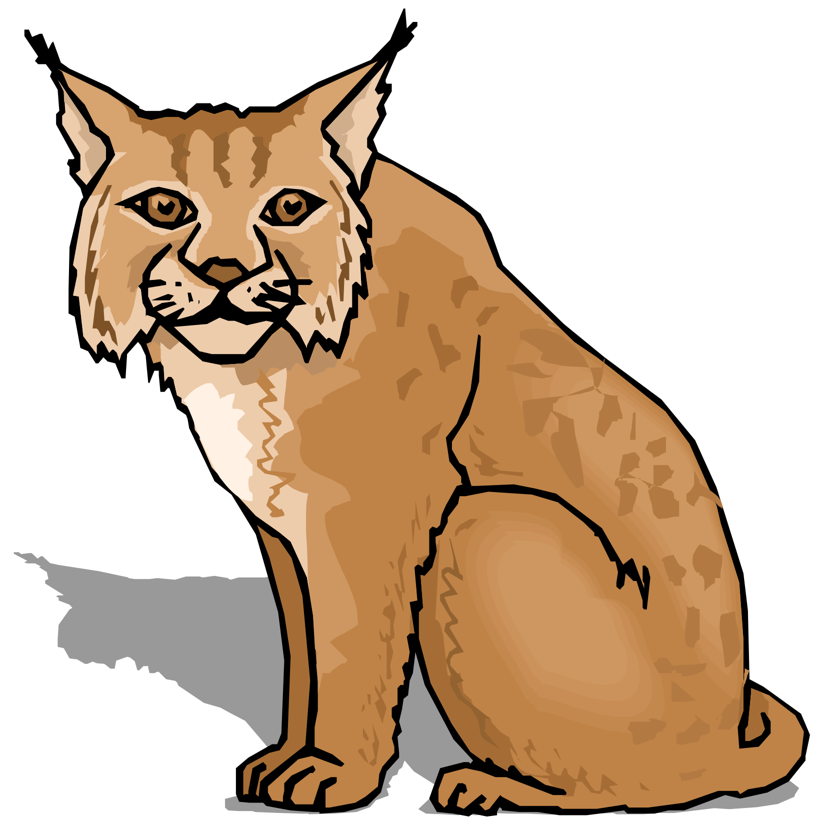
Rabbits and Lynx





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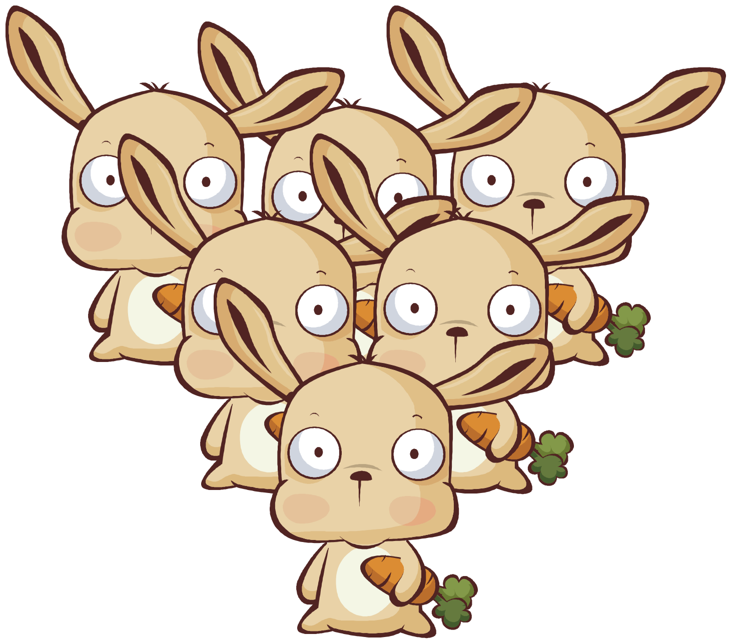
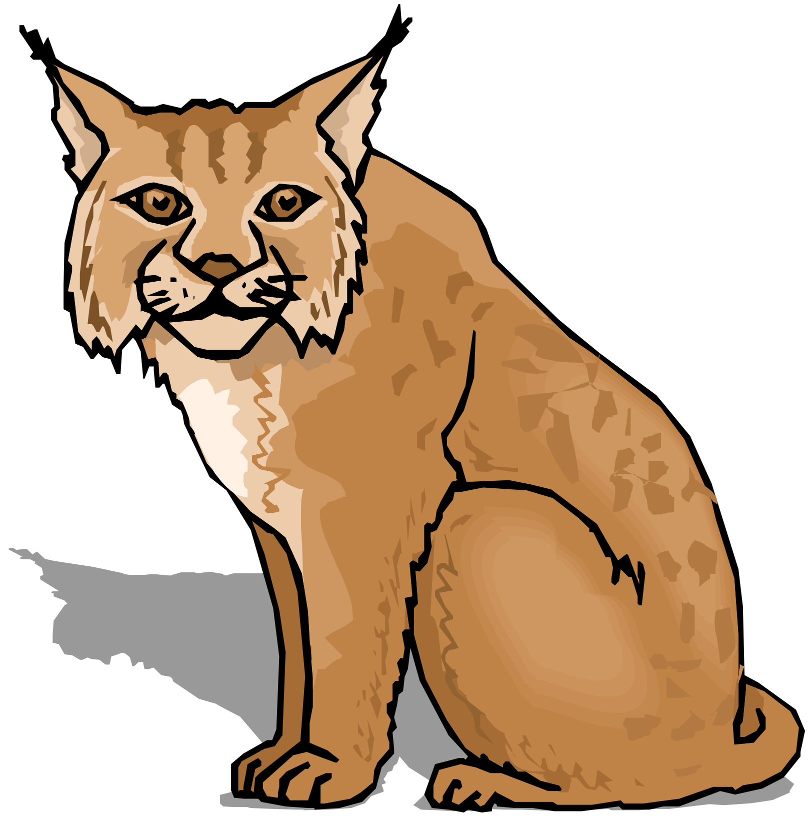
Rabbits and Lynx





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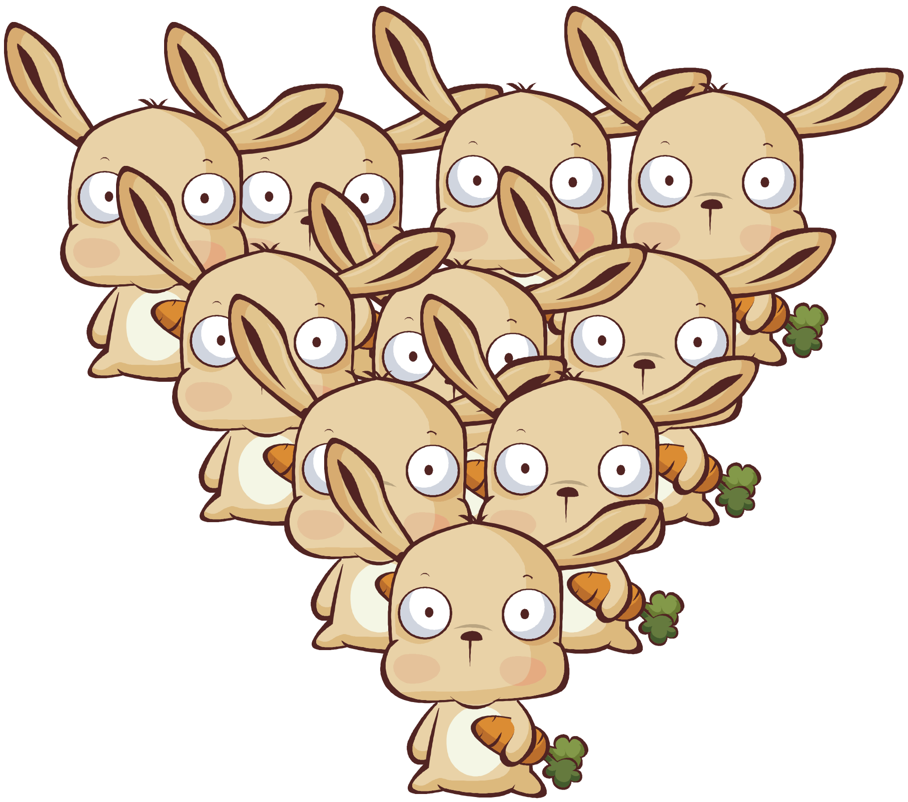
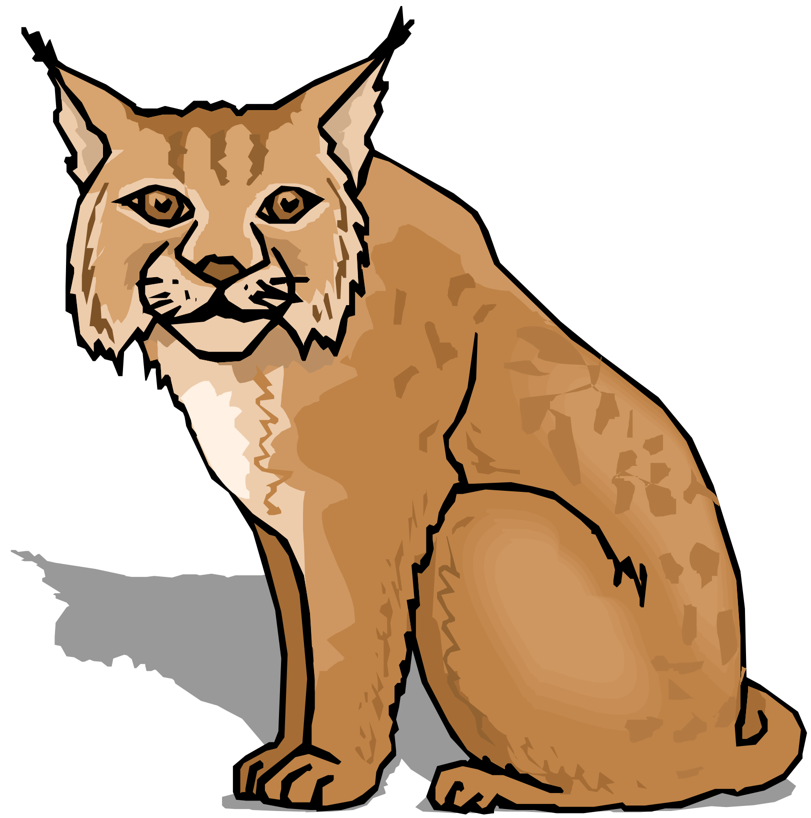
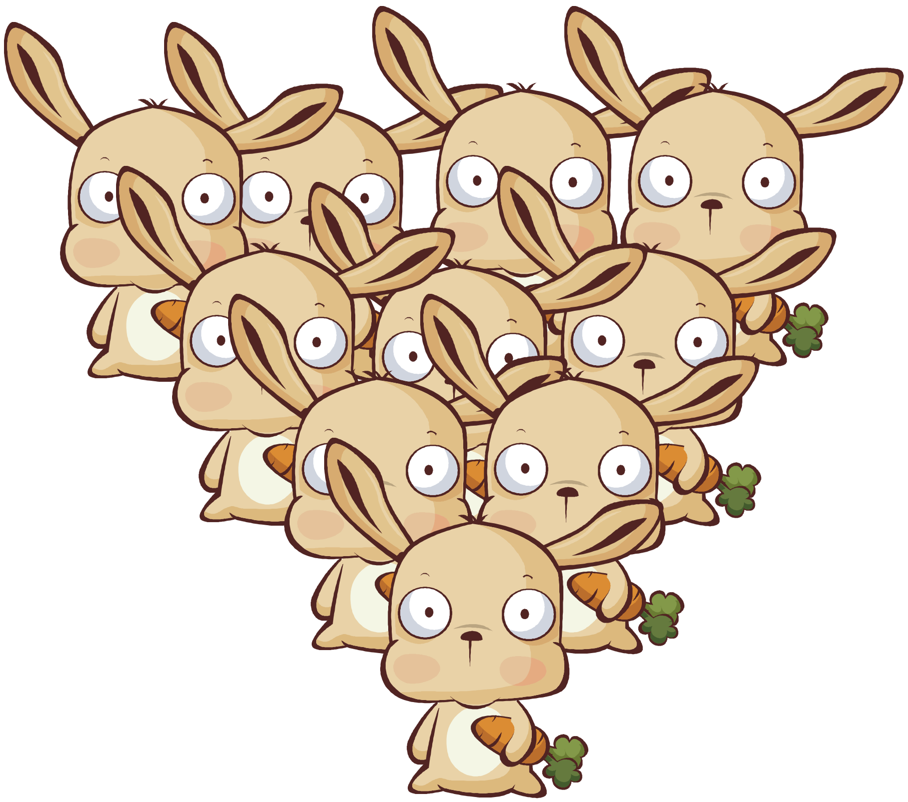
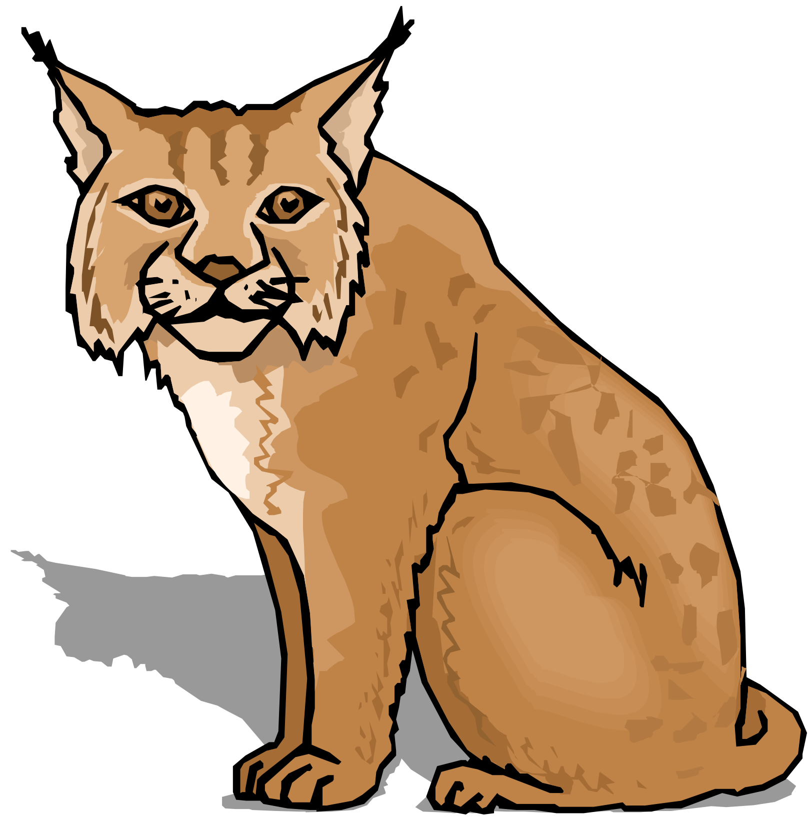




Rabbits and Lynx

- Second, lynx eat some of the rabbits





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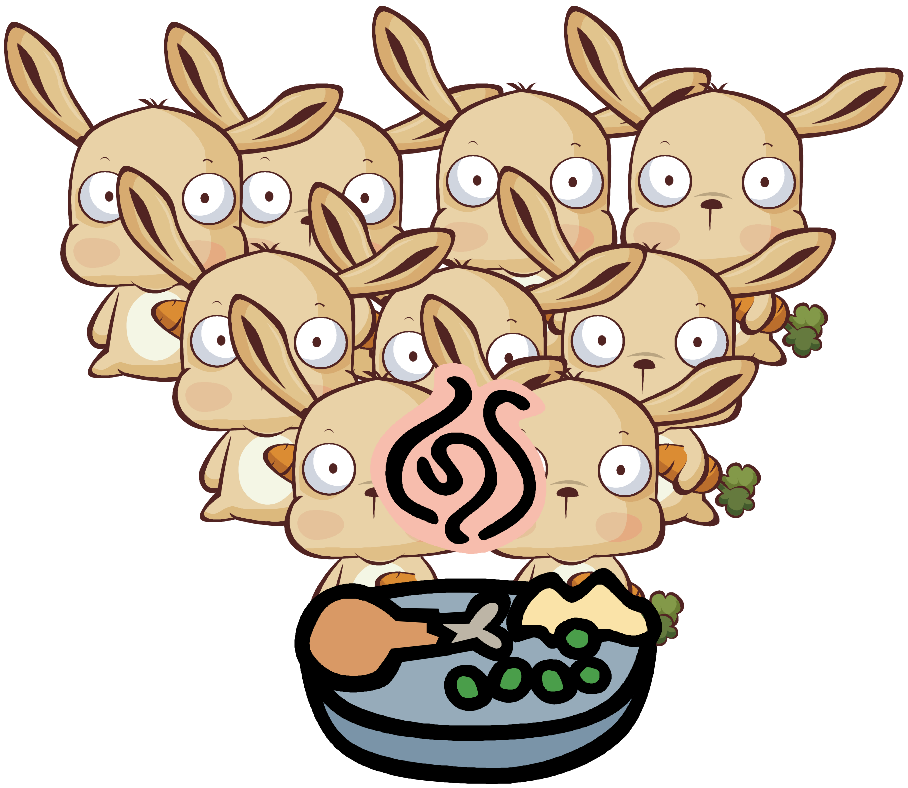
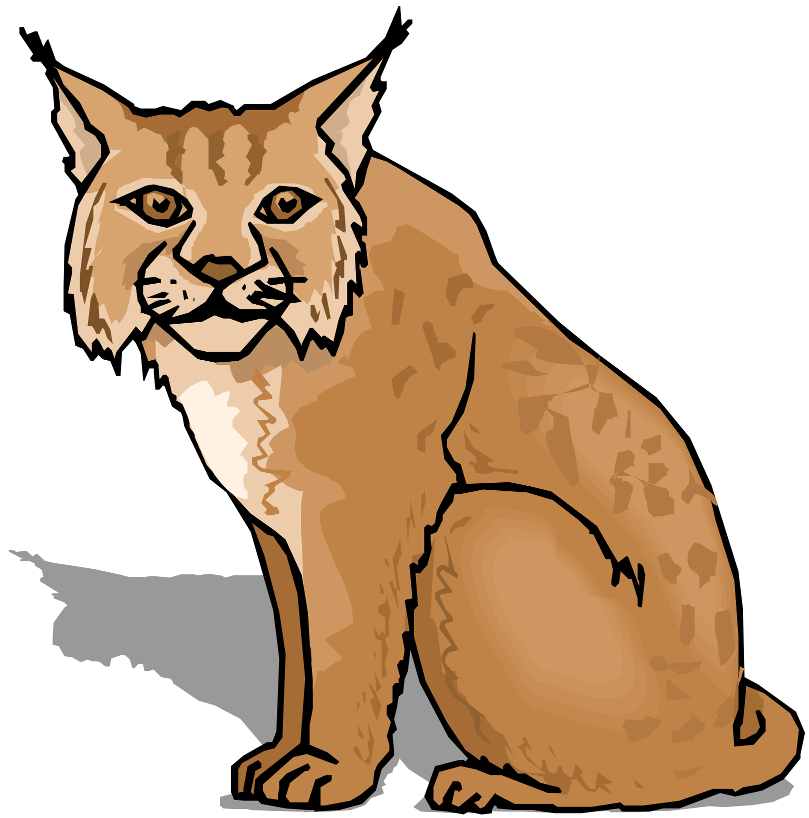
Rabbits and Lynx





- Finally, the lynx die off without rabbits to eat

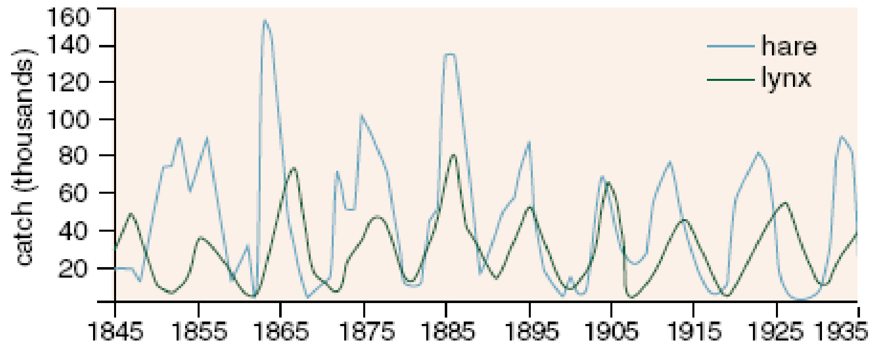
Rabbits and Lynx

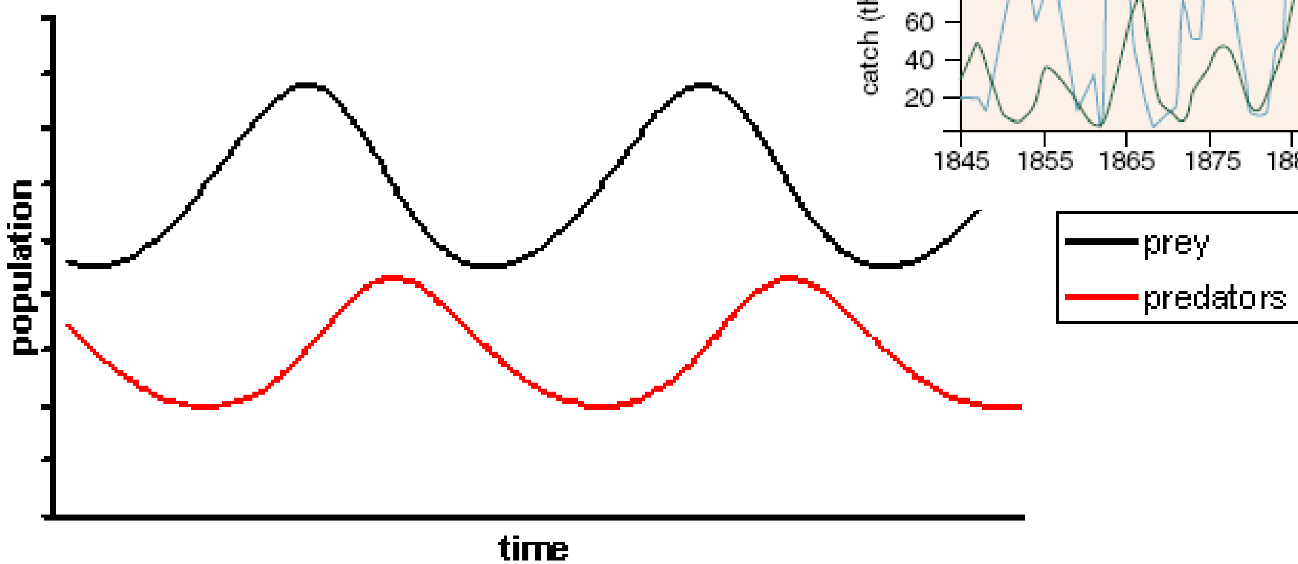
- We can write equations for the prey (x) and the predators (y)

- These simple equations give the observed behavior, even though we've neglected many things (weather, disease, distribution of rabbits and lynx, competition between lynx, etc.)

$$\frac{dx}{dt} = +\alpha x - \beta xy$$

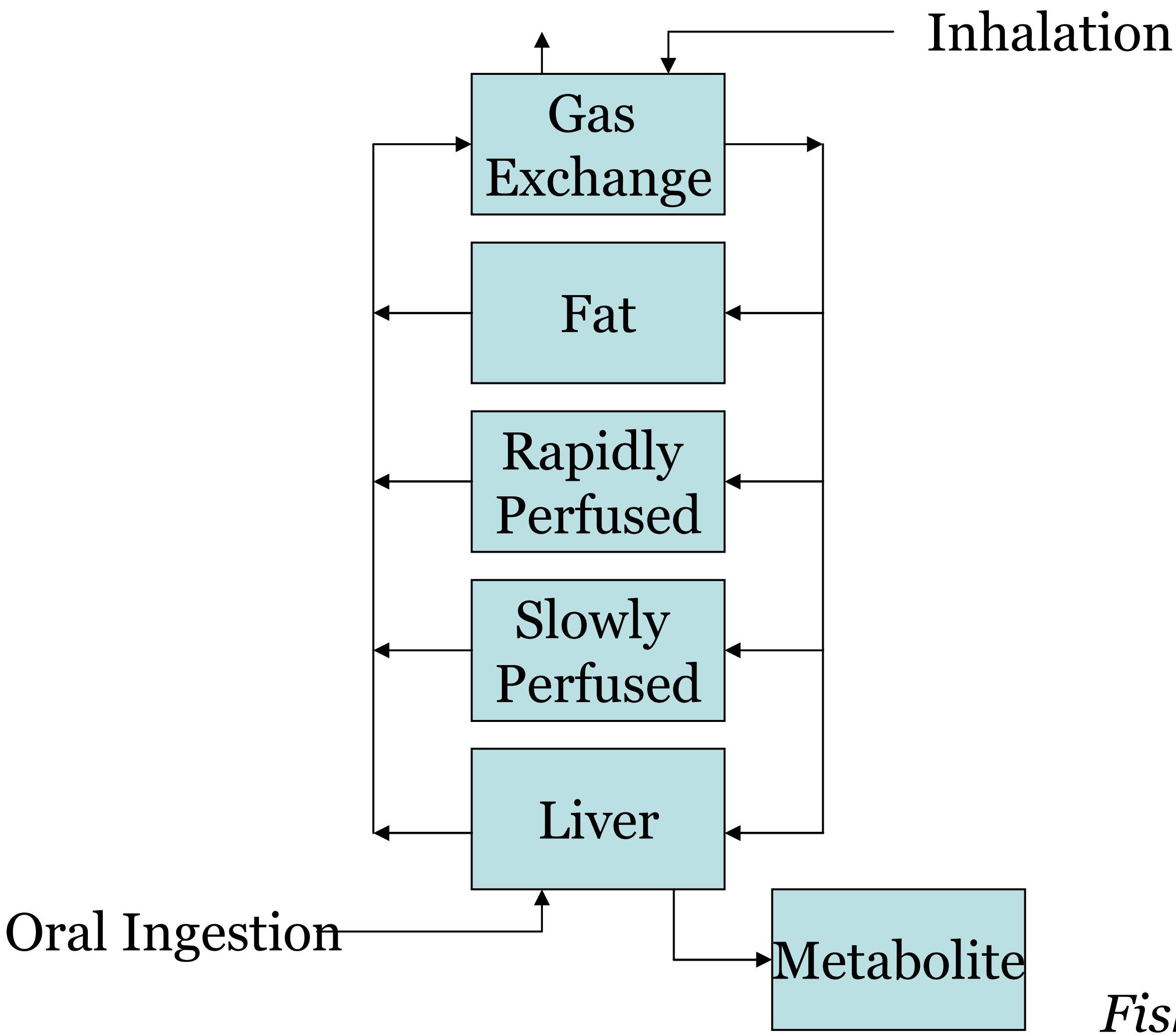
$$\frac{dy}{dt} = +\gamma xy - \delta y$$





Toxicokinetic Models

• For toxicokinetics, we can model the body as a series of linked compartments that can store a chemical:



Fisher (2000)

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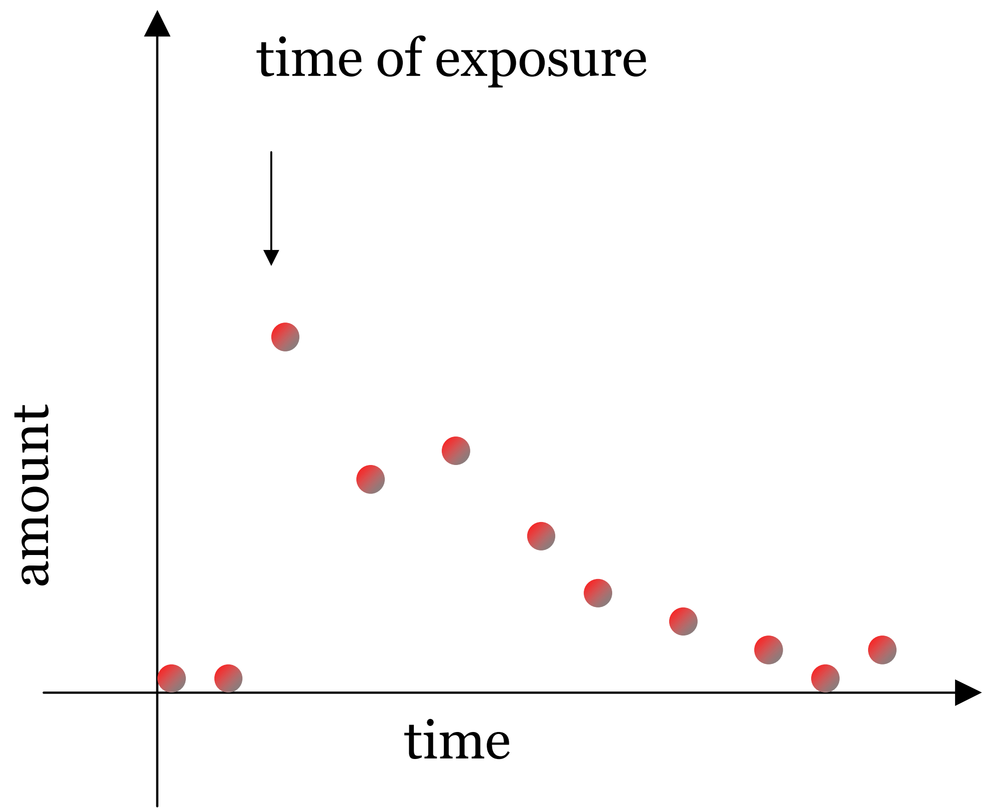
Toxicokinetic Models

• Given a set of experiments describing how much of a chemical was present after exposure, we try to find models that we can use to predict how long a certain amount of chemical stay within you and where it is stored



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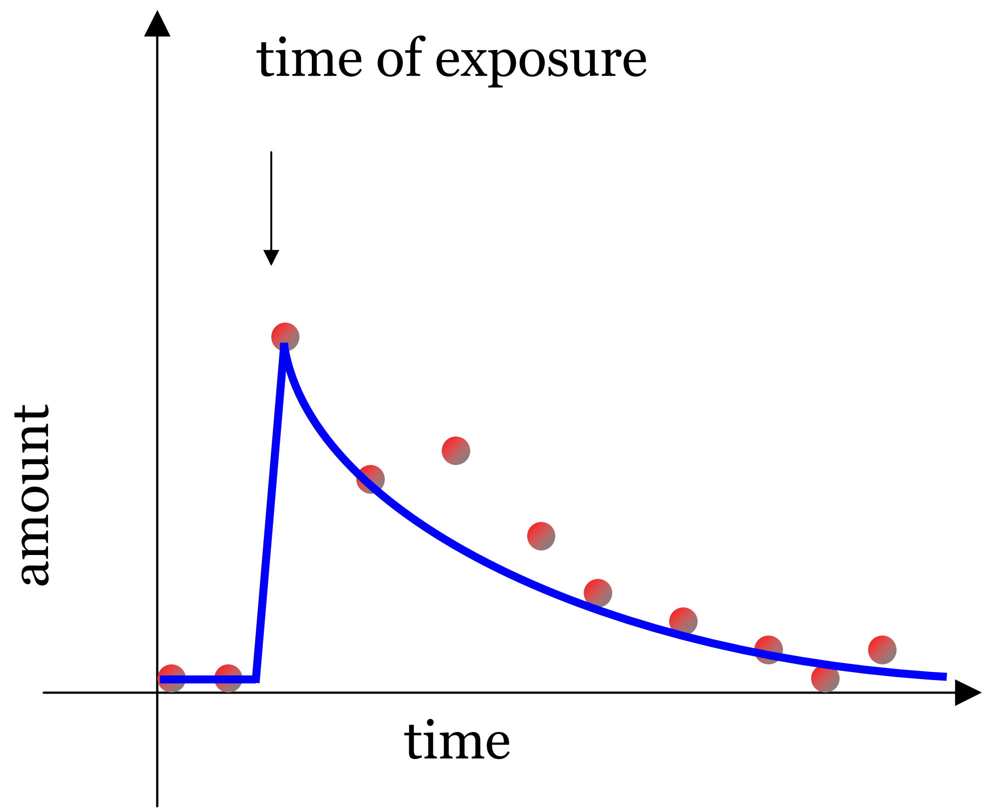

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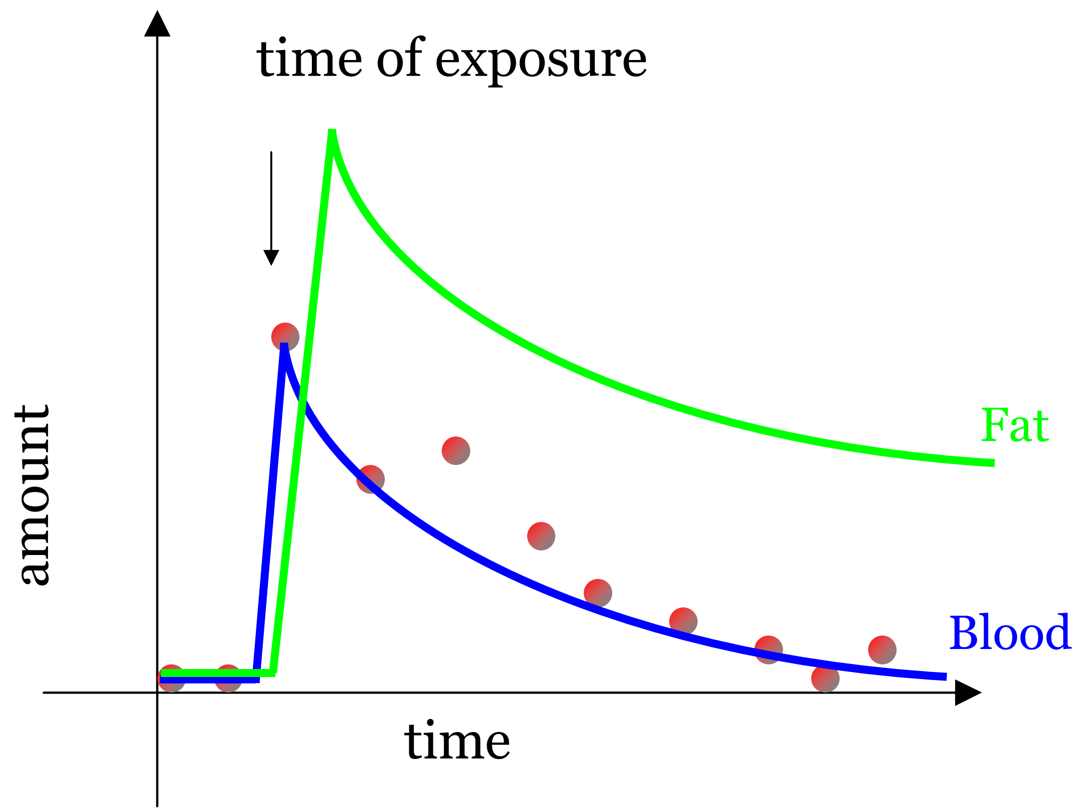

Conclusion

• Our environment is full of low levels of thousands of different chemicals

• Toxicologists are interested in what levels of those chemicals might be harmful

• One technique that is useful to understand these chemicals is biological modeling

• Models are simplifications that can allow us to understand how reality behaves